## REMARKS

### Status of the Claims

Claims 11, 12, 13, and 19-21 are pending in this application. Claims 1-8 and 14-18 have been canceled. Claims 20 and 21 have been added to recite that the active ingredients, l-menthol and an essential oil, such as peppermint oil, are synergistically effective in alleviating migraine. Support for the new claims is found in example 1 in Table 1 and the comparative examples 1 and 2 in the specification at pages 10 and 11 and Table 3. As such, no new matter has been added by the above new claims. As such, Applicants respectfully request that this Reply is entered.

### Objection to the Specification

Applicants submit herewith a Substitute Specification to correct any grammatical or typographical errors. The amendments to the specification are editorial in nature and contain no new matter. As such, Applicants respectfully request that the objection be withdrawn.

### Objection to the Claims

The Examiner objects to claims 1 and 5 as substantial duplicate claims. Applicants cancel these claims; thus, the objection is moot and should be withdrawn.

**Rejections under 35 USC 112, second paragraph**

The Examiner rejects claims 15 and 16 as indefinite. Applicants cancel claims 15 and 16; thus, the rejection is moot and should be withdrawn.

**Rejections under 35 USC 102**

The Examiner rejects claims 1, 3, 4, 5, 14 and 18 as anticipated by Karita USP 6,190,685. Applicants cancel the rejected claims; thus, the rejection should be withdrawn as moot.

The Examiner also rejects claim 2 as anticipated by Tanoue et al. USP 5,886,011. Applicants cancel the rejected claim; thus, the rejection should be withdrawn as moot.

**Rejections under 35 USC 103(a)**

The Examiner rejects 1, 3-8, 14-16 and 18 as obvious over Kamiya et al. USP 5,780,047. Applicants cancel the rejected claims; thus, the rejection should be withdrawn as moot.

The Examiner rejects claims 11-13, 17 and 19 as obvious over Goebel et al. in view of Davis et al. USP 5,665,378. Applicants traverse this rejection and respectfully request the withdrawal thereof.

Applicants submit that the present invention is directed to a method of alleviating migraine comprising the steps of administering an effective amount of a drug composition, which

consists essentially of as active ingredients l-menthol and one or more essential oils. The essential oils are lavender oil, juniper oil, peppermint oil, rose oil and rosemary oil. The active ingredients are in a pharmaceutically acceptable base to make up the drug composition. The drug composition is dermally administered to a patient suffering from migraine.

Applicants submit that the combination of Goebel and Davis fails to disclose or suggest the present invention. Goebel is concerned with alleviating headache with peppermint oil. Goebel discloses in Table 1, four preparations that were studied on healthy males. The results are shown in Table 5. The preparations contained as follows: Prep 1 → peppermint oil, eucalyptus oil and ethanol; Prep 2 → peppermint oil and ethanol; Prep 3 → eucalyptus oil and ethanol; and Prep 4 → ethanol. The study revealed that Prep 1, which contained peppermint oil, eucalyptus oil and ethanol increases cognitive performance while also having a muscle relaxing and mentally relaxing effect. <u>This preparation had little influence on pain sensitivity.</u>

In Prep 2, which contained peppermint oil and ethanol, a significant analgesic effect with a reduction in sensitivity to headache was observed.

Goebel concludes from the study that peppermint oil preparations have significant effects on mechanisms associated with the pathophysiology of clinical headache syndromes. However,

Goebel neither addresses nor answers the question of whether essential oil preparations are clinically effective in headaches aside from the described experimental laboratory mechanisms. This is noted at page 101, left column, line 7 to the last line from the bottom, which states that a double blind, placebo controlled, randomized study to compare the efficacy of the widely used analgesic paracetamol with different peppermint and eucalyptus oil preparations should be studied. (See also the Summary (last three lines) at page 93.)

Goebel never discloses or suggests that peppermint oil is effective in alleviating migraine. Goebel is only associated with headache. Moreover, Goebel never discloses or suggests the combination of peppermint oil and l-menthol as active ingredients in treating headache, much less migraine.

The secondary reference Davis discloses menthol, etc. in a drug delivery system. In Davis, menthol is not an active ingredient, but is instead used to enhance the dermal transfer of systemically active drugs. Applicants submit that an essential oil is not a systemically active drug. Furthermore, eucalyptus oil is also disclosed in Davis as a transdermal delivery enhancer.

However, according to Goebel's study report, eucalyptus alone (Prep 3) was not effective on the tested parameters, and furthermore, Prep 1 was not superior to Prep 2 even in the reduction in sensitivity to headache in spite of the fact that Prep

1 contains eucalyptus, as a skin permeation enhancer. This surely means that such permeation enhancers, such as menthol and eucalyptus as described in Davis are not relevant to the present invention.

As such, Applicants submit that there is no motivation for one of ordinary skill in the art to combine menthol and peppermint oil as active ingredients to treat migraine. Peppermint oil and menthol are not systemically active drugs as used in Davis. Peppermint oil and menthol are also not active ingredients as used in Davis. Therefore, one of ordinary skill in the art would not be motivated to use peppermint oil and menthol to alleviate migraine.

As shown in Table 3 of the present specification, the comparative examples, which contain only l-menthol as an active ingredient or peppermint oil as an active ingredient are far inferior in alleviating migraine. Please see the comparative data using volunteers, i.e. patients suffering from migraine, where the present invention, Examples 1, 3 and 5, are compared to Comparative examples 1 and 2.

Applicants submit that the Examiner is using impermissible hindsight to reconstruct the present invention. The Examiner merely relies on Applicants' own teachings to form the obviousness rejection. The Examiner has taken the present invention and divided it into two parts, i.e. part one being an essential oil, such as peppermint oil, and part two being l-menthol. The Examiner

has found each part in a separate reference associated with headache. However, neither reference suggests combining the two to arrive at the present invention namely a method of alleviating migraine. Moreover, neither reference suggests that the two can be used synergistically to alleviate migraine. This hindsight reconstruction is impermissible according to MPEP 2141 and *In re* Deminski, 796 F.2d 436, 443 230 USPQ 313, 316 (Fed. Cir. 1986).

For the foregoing reasons, Applicants submit that the present invention is patentable over Goebel in view of Davis as no prima facie case of obviousness has been established because there is no motivation to combine the references and even if there was motivation to combine the references elements of the present invention are absent from the combined teachings. Thus, Applicants respectfully request that the rejection be withdrawn and that the claims are allowed.

**Conclusion**

As Applicants have addressed and overcome all objections and rejections in the Office Action, Applicants respectfully request that the objections and rejections be withdrawn and that the claims be allowed.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $420.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kecia Reynolds (Reg. No. 47,021) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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DESCRIPTION

# DRUG FOR ALLEVIATING MIGRAINE

## TECHNICAL FIELD

The present invention relates to an external drug for dermal application, such as ointments or patches, in more detail, patches comprising in mixing l-menthol and an essential oil into a base containing a hydrophilic high-molecular weight compound, a polyhydric alcohol and water, which have a migraine-alleviating effect.

## BACKGROUND ART

The cause of migraine is not clear. It is suspected ~~but it~~ that increased ~~considered~~ blood stream due to ~~increases~~ expansion of head or cervix blood vessels caused by ~~due to~~ hormone unbalance, and ~~then muscle around that contracts. As a result migraine is caused~~ muscle contraction in the area is the cause of migraine.

For the treatment of migraine, analgesics for an internal application, which contain ergotamine tartrate, dimethothiazine mesylate, caffeine, etc., as an active ingredient are used. However, such a drug is often administered for long term and therefore, there is a possibility to induce side effects such as, anaphylaxis, insomnia, or gastrointestinal disorder.

Accordingly, various preparations for dermal applications for treating migraine have been worked out.

For example, in Japanese Patent Publication B 6-67835, a composition where ~~that~~ methysergide, an anti-serotonin, is dispersed in a hydrophilic polymer for systemic dermal application to prevent migraine is disclosed. Furthermore, in Japanese Patent Publication A Tokuhyo Hei 8-509749, a dermally therapeutic system containing sumatriptan, which is useful for migraine, cluster headache, etc., is disclosed.

However, these preparations for dermal application have a possibility to induce side effects, such as skin irritation, etc., by administering them for long term and therefore, these preparations are not favorable.

In addition, it is known that essential oils alleviate headache when used ~~in using~~ as an aromatherapy, but they ~~have a demerit being lack in simplicity on their~~ are not simple to use.

The present inventors have extensively studied in order to obviate the above mentioned demerits, and as a result, have unexpectedly found that migraine can be alleviated by dermally administering to a human a drug containing l-menthol and an essential oil as active ingredients. Thus, the present invention has been completed.

DISCLOSURE OF INVENTION

The drug having a migraine-alleviating effect of the present invention is a drug for a locally dermal application containing l-menthol and an essential oil as active ingredients. Its preferable preparations are ointments or patches, especially patches comprising ~~in mixing~~ l-menthol and an essential oil as active ingredients ~~into~~ in a base containing hydrophilic high-molecular weight compound, a polyhydric alcohol and water.

The drug of the present invention is prepared by mixing l-menthol and an essential oil with a known base and if necessary, surfactants, preservatives, etc. to make ~~into~~ ointments or patches by the conventional method.

The amount of l-menthol ~~admixed~~ is for example, 0.01% - 1% by weight per total weight of base, preferably 0.05% - 0.5% by weight per total weight of base.

The essential oils used in the present invention are lavender oil, juniper oil, peppermint oil, rose oil, rosemary oil, etc. or a mixture thereof. The amount of these oils is 0.001% - 1% by weight per total weight of base, preferably 0.005 - 0.5% by weight per total weight of base.

In ointments, known bases such as white vaseline, yellow vaseline, lanolin, purified beeswax, cetanol,

stearyl alcohol, hydrogenated oil, hydrocarbon gel, polyethylene glycol, etc. are used. To these bases, l-menthol and an essential oil and if necessary, surfactants, preservatives, purified water, etc. are mixed to prepare ointments.

The especially preferable preparations of the present invention are patch-preparations which are prepared by mixing l-menthol and an essential oil as active ingredients into the base containing a hydrophilic high-molecular weight compound, polyhydric alcohol and water.

The patches of the present invention are in more detail explained as follows.

The hydrophilic high-molecular weight compounds used in the patches include, for example, gelatin, polyacrylic acid and its salt, polyvinyl alcohol, polyvinylpyrrolidone, carboxyvinyl polymer, sodium carboxymethyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, methyl vinyl ether·maleic acid anhydride copolymer, sodium alginate, poly ethylene oxide, acacia gum, xanthan gum, tragacanth gum, etc. These may be used in a mixture thereof.

The amount of the hydrophilic high-molecular weight compound is not limited, but when its amount is less than 2% by weight per total weight of base, the base is lack in viscosity not to become paste. On the other hand, when

its amount is more than 20% by weight per total weight of base, it may occur that viscosity of the base becomes too high to smoothly prepare the preparation. Therefore, the amount of the hydrophilic high-molecular weight compound is 2-20% by weight per total weight of base, preferably 5-15% by weight per total weight of base.

The polyhydric alcohols include glycerin, sorbitol, propylene glycol, polyethylene glycol, 1,3-butylene glycol, ethylene glycol, etc. These may be used in a mixture thereof.

The amount of the polyhydric alcohol is 8 - 60% by weight per total weight of base, preferably 10 - 50% by weight per total weight of base.

When its amount is less than 8% by weight per total weight of base, humidity-keeping effect becomes poor and water become volatile in short times. On the other hand, when its amount is more than 60% by weight per total weight of base, it is difficult to mix with other substances and to use the polyhydric alcohol so much is not desirable.

The amount of water is 20 - 80% by weight per total weight of base, preferably 25 - 70% by weight per total weight of base.

When its amount is less than 20% by weight per total weight of base, dissolution of the hydrophilic high-

molecular weight compound is not satisfactory and it is impossible to homogeneously extend the base. On the other hand, when its amount is more than 80% by weight per total weight of base, it may occur that the base becomes too soft to spread out. Therefore, it is not desirable to use water so much.

The amount of l-menthol is 0.01-1% by weight per total weight of base, preferably 0.05-0.5% by weight per total weight of base as mentioned above. The amount of the essential oil is 0.001-1% by weight per total weight of base, preferably 0.005-0.5% by weight per total weight of base as mentioned above.

In addition to the above mentioned base, following additives which are usually used in patches can be mixed in the usual amount: excipients (kaolin, bentonite, titanium oxide, etc.), surfactants (glycerin fatty acid ester, polyoxyethylene castor oil, polyoxyethylene hydrogenated castor oil, sorbitan fatty acid ester, polysolbate 80, polysolbate 60, solbitan sesquioleate), crosslinking agents (multivalent metal such as aluminum hydroxide, aluminum glycinate, dihydroxyaluminum aminoacetate, synthetic hydrotalcite, etc.), coloring agents (new coccin, tartrazine, brilliant blue FCF), and preservatives (p-hydroxybenzoic acid ester, sorbic acid salt, isopropyl methyl phenol, hinokitiol, phenoxyethanol,

etc.)

The base is prepared by mixing each ingredient in accordance with the conventional method. For example, a part of a hydrophilic high-molecular weight compound and a polyhydric alcohol are dissolved in water, and if desired, other additives are mixed, and then l-menthol and an essential oil are added to the mixture to be kneaded. Then, residual of the hydrophilic high-molecular weight compound and other additives are mixed thereto to prepare the base.

The base thus prepared is spread on an appropriate support and a releasing paper is put on the base in order to protect the base. The base cut in a fixed size to prepare desired patches.

The amount of the base in patches is 200-5000g/$m^2$, preferably 500-2000g/$m^2$.

The support is one such as non-woven fabrics, fabrics, knits, etc., used in usual patches. Its material is an synthetic fiber such as nylon, rayon, polyester, polypropylene, etc. or a natural fiber such as cotton. As the releasing paper, plastic film such as polyethylene film, etc. and others used in usual patches are used.

Shapes of the patches may be ellipse, rectangle, triangle, boomerang type, facemask type, etc.

The patches of the present invention are preferably

applied to on forehead, nape of the neck, temple, a half of face and/or full face, and by doing the patch thereto, migraine-alleviating effect effectively appears.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention and its effect are illustratively explained by working examples and tests, but the invention should not be limited by these examples.

Examples 1-6

Using ingredients shown in Tables 1 and 2, patches (Examples 1-6) were prepared by the conventional method. Namely, a part of the hydrophilic high-molecular weight compound and the polyhydric alcohol were dissolved in purified water, and if necessary, other ingredients were added thereto. The mixture was fully kneaded. Then, l-menthol and the essential oil were added to the mixture and further, the residue of the hydrophilic high-molecular weight compound and other ingredients were added to. Finally, the residue of the purified water was added to the mixture. The mixture was homogeneously kneaded to prepare a base.

The base prepared was spread on the support (1000g/$m^2$) and a releasing paper or plastic film was put on it. The base was cut into a fixed size to prepare patches.

The bases prepared above, as such may be used as

ointments.

Table 1.

| Ingredients | Percent by Weight | | |
|---|---|---|---|
| | Example 1 | Example 2 | Example 3 |
| Polyacrylic acid | 1.0 | 2.5 | 1.25 |
| Sodium polyacrylate | 5.0 | 6.0 | 6.0 |
| Sodium carboxy methylcellulose | 5.0 | 4.0 | 5.5 |
| Gelatin | 0.4 | - | 0.2 |
| Polyvinyl alcohol | 0.2 | - | - |
| Tartaric acid | 0.2 | 0.15 | 0.25 |
| Disodium edetate | 0.1 | 0.08 | 0.07 |
| Glycerin | 22.0 | 15.0 | 18.0 |
| 70% Sorbitol solution | - | 15.0 | - |
| Aluminum hydroxide | 0.3 | - | - |
| Synthetic hydrotalcite | - | 0.2 | - |
| Dihyroxyaluminum acetate | - | - | 0.08 |
| Polysolbate 80 | 0.1 | 0.1 | 0.1 |
| Caster oil | 0.5 | 0.5 | 0.5 |
| Methylparaben | 0.1 | 0.1 | 0.1 |
| l-Menthol | 0.3 | 0.15 | 0.1 |
| Peppermint oil | 0.2 | - | - |
| Rose oil | - | 0.1 | - |
| Lavender oil | - | - | 0.01 |
| Purified water | Residue | Residue | Residue |
| | 100 | 100 | 100 |

Table 2.

| Ingredients | Percent by Weight | | |
|---|---|---|---|
| | Example 4 | Example 5 | Example 6 |
| Polyacryric acid | 1.5 | 2.0 | 1.25 |
| Sodium polyacrylate | 5.0 | 5.5 | 6.0 |
| Sodium carboxy methylcellulose | 5.0 | 4.0 | 5.5 |
| Gelatin | - | - | - |
| Polyvinyl alcohol | 0.2 | - | - |
| Tartaric acid | 0.2 | 0.15 | 0.3 |
| Disodium edetate | 0.1 | 0.08 | 0.07 |
| Glycerin | 20.0 | 15.0 | 20.0 |
| 70% Sorbitol solution | 10.0 | 15.0 | - |
| Aluminum hydroxide | 0.3 | - | - |
| Synthetic hydrotalcite | 0.15 | - | - |
| Dihydroxyaluminum acetate | - | 0.1 | 0.1 |
| Polysolbate 80 | 0.1 | 0.1 | 0.1 |
| Caster oil | 0.5 | 0.5 | 0.5 |
| Methylparaben | 0.1 | 0.1 | 0.1 |
| l-Menthol | 0.8 | 0.25 | 0.05 |
| Peppermint oil | 0.2 | 0.4 | - |
| Rose oil | - | 0.4 | 0.05 |
| Lavender oil | 0.05 | - | 0.1 |
| Purified water | Residue | Residue | Residue |
| | 100 | 100 | 100 |

Comparative example 1

The patch was prepared by the same method as Example

1 using the same ingredients as Example 1 provided that the same amount of water as l-menthol was used instead of l-menthol (Only an essential oil is used as an active ingredient).

Comparative example 2

The patch was prepared by the same method as Example 1 using the same ingredients as Example 1 provided that the same amount of water as an essential oil was used instead of the essential oil (Only l-menthol is used as an active ingredient).

Comparative example 3

The patch was prepared by the same method as Example 1 using the same ingredients as Example 1 provided that the same amount of water was used instead of the essential oil and l-menthol (Any active ingredient was not used).

Next, each two patches (5x7cm) of Examples 1, 3, 5 and Comparative examples 1-3 were put on each volunteer. The following items were sensitively evaluated.

Test 1

On their foreheads of ten volunteers suffering from migraine were put each patch of Examples 1, 3, 5 and

Comparative examples 1-3, and migraine-alleviating effect was evaluated by sensory test under following evaluation-standards.

Evaluation-standard on effects

Point 1: no effect

Point 2: weak effect

Point 3: effective

Point 4: clearly effective

Point 5: strongly effective

Efficacy (point) was indicated by the average of volunteer's evaluations. The duration of the effect was indicated by the average of volunteer's reported times.

The result was shown in the following Table 3.

Table 3

| | Efficacy(point) | Duration of effect(hour) |
|---|---|---|
| Example 1 | 4.2 | 7.3 |
| Example 3 | 4.3 | 7.9 |
| Example 5 | 3.9 | 6.5 |
| Comparative example 1 | 2.5 | 3.2 |
| Comparative example 2 | 2.8 | 2.8 |
| Comparative example 3 | 1.3 | 2.1 |

As is clear from the result of Table 3, patches of

Examples 1, 3 and 5 were superior in efficacy (point) to patches of Comparative examples 1-3, and therefore, it is recognized that patches of Examples 1, 3 and 5 are excellent in migraine-alleviating effect and that its effect lasts for long hours.

Test 2

On various regions of ten volunteers suffering from migraine were put each patch of Examples 1, 3, 5 and Comparative example 3, and migraine-alleviating effect depending on the region was evaluated by sensory test under following evaluation-standards.

Evaluation standard:

+ : Positive alleviating efficacy

± : Weak alleviating efficacy

- : No alleviating efficacy

The result is shown in Table 4.

Table 4.

| Application region | Alleviating efficacy | | | |
|---|---|---|---|---|
| | Example 1 | Example 3 | Example 5 | Comparative example 3 |

| | | | | |
|---|---|---|---|---|
| Forehead | + | + | + | ± |
| Nape of neck | + | + | + | - |
| Temple | + | + | + | ± |
| Shoulder | ± | ± | ± | - |
| Back | - | - | - | - |
| Breast | - | - | - | - |

As is clear from the result of Table 4, when applying the preparations of the present invention, that is preparations of Examples 1, 3 and 5 to face, nape of the neck and temple, the preparations were recognized being superior in migraine-alleviating efficacy. On the other hand, a patch of Comparative example 3 hardly showed migraine-alleviating efficacy in any region.

INDUSTRIAL APPLICABILITY

The preparation of the present invention is excellent in migraine-alleviating efficacy, and even when using for long terms, there is hardly a possibility to induce side effects and the preparation of the present invention is very convenient and useful.